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INCYTE CORPORATION
EXPERIMENTAL STATION
ROUTE 141 & HENRY CLAY ROAD
BLDG. E336
WILMINGTON, DE 19880

| EXAMINER | |
|---|---|
| LANDSMAN, ROBERT S | |
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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Paper No. 12

Application Number: 09/997,522
Filing Date: November 28, 2001
Appellant(s): COLEMAN ET AL.

Terence Lo
For Appellant

**SUPPLEMENTAL EXAMINER'S ANSWER**

This is in response to the appeal brief filed 6/27/03. This revised Examiner's Answer is only to correct minor errors and does not contain any new rejections or new arguments. The only corrections made were to section (9) Prior Art of Record. U.S. Patents Coleman 5,686,597 and 5,869,633 were added and Ayala et al. and Rieger et al. were deleted.

*(1) Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

*(2) Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

*(3) Status of Claims*

The statement of the status of the claims contained in the brief is correct.

*(4) Status of Amendments After Final*

No amendment after final has been filed.

*(5) Summary of Invention*

The summary of invention contained in the brief is correct.

*(6) Issues*

The appellant's statement of the issues in the brief is correct.

*(7) Grouping of Claims*

The appelants provide a statement in the brief that the claims stand or fall together.

*(8) Claims Appealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

*(9) Prior Art of Record*

Skolnick, J. et al "From genes to protein structure and function:novel applications of computational approaches in the genomic era." Trends in Biotech, vol 18, no. 1 (2000), pp. 34-39

Bork, P. "Powers and pitfalls in sequence analysis:the 70% hurdle." Genome Research, vol. 10 (2000), pp. 398-400.

Doerks, T, et al. "Protein annotation:detective work for function prediction." Trends in Genetics, vol 14, No. 6 (June 1998), pp. 248-250.

Smith, TF, et al. "The challenges of genome sequence annontation or "the devil is in the details." Nature Biotechnology, vol. 15 (November 1997), p. 1222-1223.

Brenner, SE. "Errors in genome annotation." Trends in Genetics, vol. 15, No. 4 (April 1999), p. 132.

Bork, P. et al. "Go hunting in sequence databases but watch out for the traps." Trends in Genetics, vol. 12, No. 10 (October 1996), pp. 425-427.

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| 5,686,597 | Coleman el al. | 11-1997 |
| 5,869,633 | Coleman et al. | 2-1999 |

Soukhanov, AH, et al. New Riverside University Dictionary. The Riverside Publishing Co. 1988, p. 646 and page 956.

*(10) Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

(a) Claims 3-7, 9, 10, 12, 13, 57 and 58 are rejected under 35 USC 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. This rejection is set forth in the prior Office Action dated 9/3/02 (Paper No. 6). As stated therein: the claims are directed to an isolated polynucleotide of SEQ ID NO:1 which encodes a thrombin receptor of SEQ ID NO:2, or fragments thereof, as well as transformed cells and methods for making this protein. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated polynucleotide encoding a protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

It is clear from the instant specification that the claimed receptor is what is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the protein encoded for by the claimed polynucleotide, or its significance. Applicants disclose in the specification that this receptor is believed to be a thrombin receptor. However, the basis that the receptor encoded for by the polynucleotide of the present invention is only known to be homologous to thrombin receptors (page 2, lines 21-26 of the specification) is not predictive of a use. There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicants' claimed invention is incomplete.

The instant situation is directly analogous to that of which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form – there is insufficient justification for

permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

The specification discloses that the polynucleotide of the invention encodes a protein which has significant sequence similarity to two different receptors - a known human thrombin receptor and only partial homology to a platelet activating receptor (page 2, lines 21-26 of the specification). Based on the structural similarity, the specification asserts that the newly disclosed SEQ ID NO:1 and 2 have similar activities to the thrombin receptor (page 5, lines 20-21). The assertion that the disclosed proteins have biological activities similar to known thrombin receptors cannot be accepted in the absence of supporting evidence, because generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene.

Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of the claimed polynucleotide of SEQ ID NO:1 which encodes the protein of SEQ ID NO:2, which is only known to be homologous to thrombin receptors. Therefore, the instant claims are drawn to a polynucleotide encoding a

protein which has a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

Furthermore, since the nucleic acid (SEQ ID NO:1) and protein (SEQ ID NO:2) of the invention are not supported by a specific and substantial asserted utility or a well established utility, the host cell, method for producing the protein, the polynucleotide encoding thrombin-binding and immunogenic fragments as well as naturally occurring variants of said sequences and polynucleotides comprising at least 60 contiguous bases of SEQ ID NO:1, or of said variants also lack utility.

(b) Claims 3-7, 9, 10, 12, 13, 57 and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(c) Furthermore, even if the invention possessed utility under 35 USC 101, claims 3, 6, 7, 9, 12, 13 and 58 would be rejected under 35 U.S.C. 112, first paragraph, because the specification, while then being enabling for SEQ ID NO:1 and 2, does not reasonably provide enablement for polynucleotides encoding thrombin-binding fragments of SEQ ID NO:2, naturally occurring human variants of SEQ ID NO:1 or 2, or at least 60 contiguous nucleotides of a naturally occurring human variants of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive with regard to claiming all polynucleotides which are "naturally occurring human variants" of SEQ ID NO:1. Polynucleotides which encode proteins which are naturally occurring human variants of SEQ ID NO:2, or are "at least 60 contiguous nucleotides" of a naturally occurring human variants of SEQ ID NO:1, would have one or more nucleic acid substitutions, deletions, insertions and/or additions to SEQ ID NO:1 and these proteins would have one or more amino acid substitutions, deletions, insertions and/or additions to the protein encoded for by SEQ ID NO:2. Similarly, "thrombin-binding fragments" of SEQ ID NO:2 would also have one or more amino acid deletions to SEQ ID NO:2.

Applicants provide no guidance or working examples of polynucleotides which are "naturally occurring human variants" of SEQ ID NO:1, or which encode SEQ ID NO:2, nor do they provide a *function* of these variants. Similarly, Applicants do not provide any guidance or working examples of thrombin-binding fragments. Applicants have not taught the artisan how to identify a naturally occurring human variant of SEQ ID NO:1 or 2, or what critical residues are necessary to maintain the function of a variant of this protein, or how to determine whether or not a protein, or its encoding polynucleotide, is considered a naturally occurring human variant, nor do they teach what residues are required in order to maintain the thrombin-binding characteristics of SEQ ID NO:2. No residues necessary for the binding of thrombin to SEQ ID NO:2 have been identified. Furthermore, it is not predictable to one of ordinary skill in the art how to identify a naturally occurring human variant of SEQ ID NO:1 or 2, or what critical residues are necessary to maintain the function of a variant of SEQ ID NO:2, or to determine whether or not a protein, or its encoding polynucleotide, is considered a naturally occurring human variant, nor is it predictable to the artisan what residues are required to maintain the thrombin-binding characteristics of SEQ ID NO:2.

Furthermore, the claims include in scope allelic variants of the disclosed thrombin molecules. The Examiner notes, though allelic variants are not specifically defined in the specification, the phrase "naturally occurring TRH," which is defined on page 5 of the specification as "...TRHs produced by human cells that have not been genetically engineered...", reads on allelic variants. The Examiner cannot determine how one would distinguish, merely by examination of the protein, whether a protein were the result of expression of a different allele, or alternatively, were merely one of a number of ultimate species that might be obtained by the expression of SEQ ID NO:1 disclosed in this application. Enablement is not commensurate in scope with claims to proteins potentially encoded for by allelic variants of SEQ ID NO:1, or those of SEQ ID NO:2. Allelic variants often encode proteins with quantitatively or qualitatively altered or absent biological activity. Therefore, the specification does not teach how to use such variants,

nor is adequate guidance provided for the skilled artisan to predict, *a priori*, which variants would reasonably be expected to retain biological function.

In summary, the breadth of the claims is excessive with regard to claiming all polynucleotides which are "naturally occurring human variants" of SEQ ID NO:1, those which encode SEQ ID NO:2, or those which comprise at least 60 contiguous bases thereof. There is also a lack of guidance and working examples of these nucleic acid molecules and proteins as well as a lack of guidance, working examples and predictability how to identify a naturally occurring human variant of SEQ ID NO:1 or 2, or what critical residues are necessary to maintain the function of this variant protein or of a thrombin-binding fragment of SEQ ID NO:2, or to determine whether or not a protein, or its encoding polynucleotide, is considered a naturally occurring human variant. For this reason, the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

(d) Claims 3, 6, 7, 9, 12, 13 and 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. Polynucleotides which are, or which encode, naturally occurring human variants of SEQ ID NO:1 or 2, or polynucleotides of at least 60 contiguous bases thereof, would have one or more nucleic acid substitutions, deletions, insertions and/or additions to the polynucleotide of SEQ ID NO:1, or more amino acid substitutions, deletions, insertions and/or additions to the protein of SEQ ID NO:2. Similarly, thrombin-binding fragments of SEQ ID NO:2 would also have one or more amino acid substitutions, deletions, insertions and/or additions to the protein of SEQ ID NO:2.

The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes are made to SEQ ID NO:1 or 2 to be considered a naturally occurring human variant, or what residues of SEQ ID NO:2 constitute a thrombin-binding fragment. Structural features that could distinguish compounds in the genus from others in the polynucleotide or protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:1 and 2 alone are insufficient to describe the genus.

One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

(e) Claims 4, 5 and 57 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 or 3 of prior U.S. Patent No. 5,686,597. This is a double patenting rejection. Claim 4 of the present application recites an isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2. Claim 1 of the patent recites an isolated polynucleotide encoding a thrombin receptor homolog of SEQ ID NO:2. Though claim 4 of the application does not recite "thrombin receptor homolog," since the sequences are 100% identical, they would inherently encode the same protein. Therefore, one of ordinary skill in the art would immediately envision that the encoded proteins of both the patent and application are the same. Claims 5 and 57 of the present application recite an isolated polynucleotide comprising the polynucleotide sequence of SEQ ID NO:1. Claim 3 of the patent recites a recombinant DNA molecule comprising SEQ ID NO:1. Though neither claims 5 nor 57 of the application recite that the polynucleotide is "recombinant," one of ordinary skill in the art would not be able to differentiate a "recombinant" polynucleotide from a "non-recombinant" polynucleotide since they would have the same inherent structure. Therefore, one of ordinary skill in the art would immediately envision the that the polynucleotides of claims 5 and 57 of the application could be recombinant and, therefore, identical to that of claim 3 of the patent.

(f) Claims 3, 4, 5, 12, 13 and 57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,869,633. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 3 and claim 4 of the present application recite an isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2. Claim 5 of the present application recites an isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2 wherein the polynucleotide is SEQ ID NO:1. Claim 12 recites a polynucleotide comprising SEQ ID NO:1. Claim 13 recites a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:1. Claim 57 recites the polynucleotide of SEQ ID NO:1. Claim 1 of the patent recites an isolated polynucleotide complementary to a polynucleotide encoding the polypeptide of SEQ ID NO:2. SEQ ID NO:2, as recited in the patent, is encoded for by SEQ ID NO:1, as recited in the application (see the specific disclosure in column 4, lines 21-26 of the patent). Though the claims of the application do not recite "thrombin

receptor homolog," since SEQ ID NO:1 and 2 are 100% identical in both the patent and application, they would inherently encode the same protein. Therefore, one of ordinary skill in the art would immediately envision that the encoded proteins of both the patent and application are the same. Given the claimed complement (i.e. antisense) of a polynucleotide encoding SEQ ID NO:2, as recited in the patent, one of ordinary skill in the art would immediately envision the sense strand to this polynucleotide, which would encode SEQ ID NO:2 and which includes that of SEQ ID NO:1 of the present application. In addition, the sense strand of a polynucleotide encoding SEQ ID NO:2, as recited in the patent, would encode a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:1, as recited in the application, especially given that the claim of the patent does not recite that the complement is "fully complementary."

Given that it was known that SEQ ID NO:1 encodes SEQ ID NO:2, it would have been obvious for one of ordinary skill in the art to have obtained the sense strand to a complement of a polynucleotide encoding SEQ ID NO:2, including SEQ ID NO:1 since, not only is this the strand which encodes for a protein, but the sense strand would be required in order for the artisan to produce recombinant expression vectors, host cells and the protein of interest since the antisense strand, alone, would not be able to produce the protein of interest. The artisan would have been motivated to produce the sense strand to the complement recited in the patent in order to amplify the polynucleotide and to produce the encoded protein for binding and functional assays in order to identify compounds which can be used in the treatment of human diseases involving this protein. There would have been a high expectation of success in obtaining this sense strand to the complement of the patent since DNA cloning and amplification techniques were well-known and highly successful in the art at the time of the present invention.

Similarly, it would have been obvious for one of ordinary skill in the art to make a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:1 to use as a hybridization probe to identify DNA encoding homologous receptors, or for tissue typing or chromosomal localization. This information would help to further characterize the polynucleotide and protein of the present invention and help to further elucidate molecular mechanisms of these molecules in an organism. There would have been a high expectation of success in producing and using these polynucleotides since DNA cloning, amplification and hybridization techniques were well-known and highly successful in the art at the time of the present invention.

(g) Claims 3, 12 and 13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,686,597. Claim 4 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. 5,686,597. Claims 5 and 57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,686,597. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 3 and 4 of the present application recite an isolated polynucleotide encoding the protein of SEQ ID NO:2, which reads on claim 3 of the patent since claim 3 recites a recombinant DNA comprising SEQ ID NO:1. SEQ ID NO:1 encodes SEQ ID NO:2.

Claim 5 of the present application recites an isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2 wherein the polynucleotide is SEQ ID NO:1, and claims 12 and 57 recites the polynucleotide of SEQ ID NO:1, both of these claims read on claim 1 of the patent since claim 1 recites an isolated polynucleotide encoding a thrombin receptor homolog of SEQ ID NO:2. Claim 13 recites a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:1. Claim 1 of the patent recites an isolated polynucleotide encoding a thrombin receptor homolog comprising the amino acid sequence of SEQ ID NO:2. Claim 3 of the patent recites the polynucleotide of SEQ ID NO:1. Therefore, claim 3 of the patent would encode a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:1, as recited in the application.

Though the claims of the application do not recite "thrombin receptor homolog," since the sequences are 100% identical, they would inherently encode the same protein. Therefore, one of ordinary skill in the art would immediately envision that the encoded proteins of both the patent and application are the same.

It would have been obvious for one of ordinary skill in the art to make a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:1 to use as a hybridization probe to identify DNA encoding homologous receptors, or for tissue typing or chromosomal localization. This information would help to further characterize the polynucleotide and protein of the present invention and help to further elucidate molecular mechanisms of these molecules in an organism. For these reasons it would have also been obvious to the artisan, given either SEQ ID NO:1 or 2, to obtain all DNA encoding SEQ ID NO:2 in order to have a complete record of all the polynucleotides which encode SEQ ID NO:2 which will aid in understanding of the differences in these polynucleotides and potential mutational sites which exist in these polynucleotides between individuals which are predisposed to disease. There would have been a high expectation of success in producing and using these polynucleotides since DNA cloning,

amplification and hybridization techniques were well-known and highly successful in the art at the time of the present invention.

(h) Claim 6 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 5,686,597. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 6 of the present application recites a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding SEQ ID NO:2. Claim 2 of the patent recites a polynucleotide encoding SEQ ID NO:2 further comprising a control sequence. Though claim 6 of the application does not recite "thrombin receptor homolog," since the sequences are 100% identical, they would inherently encode the same protein. Therefore, one of ordinary skill in the art would immediately envision that the encoded proteins of both the patent and application are the same. However, claim 6 of the application recites "promoter" and claim 2 of the patent recites "control sequence."

Though not all control sequences are promoters, it would have been obvious for one of ordinary skill in the art to have used a promoter for the control sequence of the patent in order to allow for the protein encoded for by the polynucleotide of the invention to be expressed. The artisan would have been motivated to use a promoter in order to not only aid in expression of the protein of interest, but to express this protein in a larger quantity than otherwise may be produced in the absence of a promoter in order to produce the encoded protein for binding and functional assays in order to identify compounds which can be used in the treatment of human diseases involving this protein. There would have been a high expectation of success in using a promoter along with the polynucleotide of the patent since DNA cloning and amplification techniques were well-known and highly successful in the art at the time of the present invention.

(i) Claims 9 and 10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of U.S. Patent No. 5,686,597. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9 and 10 of the present application recite a method of producing the polypeptide of SEQ ID NO:2. Claim 6 of the patent recites a method of producing the thrombin receptor homolog of SEQ ID NO:2. Though claims 9 and 10 of the application do not recite "thrombin receptor homolog," since the sequences are 100% identical, they would inherently encode the same protein. Therefore, one of ordinary skill in the art would immediately envision that the encoded proteins of both the patent and application are the same. However,

claims 9 and 10 of the application recite the use of a "promoter" and the patent recites the use of an "expression vector."

Though not all expression vectors require a promoter, it would have been obvious for one of ordinary skill in the art to have used a promoter in the expression vector of the patent in order to allow for the protein encoded for by the polynucleotide of the invention to be expressed. The artisan would have been motivated to use an expression vector with a promoter in order to not only express the protein of interest, but to express this protein in a larger quantity than otherwise may be produced in an expression vector without a promoter in order to produce the encoded protein for binding and functional assays in order to identify compounds which can be used in the treatment of human diseases involving this protein. There would have been a high expectation of success in using expression vectors comprising promoters since DNA cloning and amplification techniques were well-known and highly successful in the art at the time of the present invention.

(j) Claims 6 and 7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4 and 5, respectively, of U.S. Patent No. 5,686,597. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 6 of the present application recites a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding SEQ ID NO:2. Claim 7 of the application recites a cell transformed with the polynucleotide of claim 6. Claim 4 of the patent recites an expression vector comprising the polynucleotide of SEQ ID NO:1. Claim 5 of the patent recites a host cell comprising SEQ ID NO:1.

Though neither claims 4 or 5 of the patent recite that the polynucleotide is "recombinant," one of ordinary skill in the art would not be able to differentiate a "recombinant" polynucleotide from a "non-recombinant" polynucleotide since they would have the same inherent structure. Therefore, one of ordinary skill in the art would immediately envision the that the polynucleotides of claims 4 and 5 of the patent could be recombinant and, therefore, identical to the polynucleotide of claim 6 and 7 of the application. Though the claims of the application do not recite "thrombin receptor homolog," since the sequences are 100% identical, they would inherently encode the same protein. Therefore, one of ordinary skill in the art would immediately envision that the encoded proteins of both the patent and application are the same. Similarly, claims 4 and 5 of the patent recite the use of an "expression vector" whereas the application recites the use of a "promoter."

Though not all expression vectors require a promoter, it would have been obvious for one of ordinary skill in the art to have used a promoter in the expression vector of the patent in order to allow for

the protein encoded for by the polynucleotide of the invention to be expressed. The artisan would have been motivated to use an expression vector with a promoter in order to not only express the protein of interest, but to express this protein in a larger quantity than otherwise may be produced in an expression vector without a promoter in order to produce the encoded protein for binding and functional assays in order to identify compounds which can be used in the treatment of human diseases involving this protein. There would have been a high expectation of success in using expression systems comprising promoters since DNA cloning and amplification techniques were well-known and highly successful in the art at the time of the present invention.

*(11) Response to Argument*

(a) Regarding the rejection of the claims under 35 USC 101 (paragraph (a) above), Applicants argue that the claimed polynucleotide encodes a human homolog of a thrombin GPCR. However, they also state that this protein is also homologous to platelet activating factor (PAF) receptor. Applicants argue that the general biological functions of GPCRs are well-known and that the functions of thrombin receptors are also known. Applicants' arguments that the receptor of the present invention is homologous to both thrombin and PAF receptor and, therefore, a member of the GPCR superfamily, and would have utility because it is a GPCR, is not deemed persuasive. The basis that the receptor encoded for by the polynucleotide of the present invention (or its transmembrane domains and intracellular loops) is only known to be homologous to thrombin receptors (page 2, lines 21-26 of the specification) is not predictive of a use. Therefore, in the absence of further characterization of the protein of the present invention, it is not clear to what subfamily of GPCRs the protein of the present invention belongs. Applicants further state that the Declaration under 37 CFR 1.131 by Lars Michael Furness (Furness Declaration) makes it clear that GPCRs (T7Gs) are targets of many current drug treatments. Again, simply knowing that the protein of the present invention is a GPCR is not sufficient to establish a specific or substantial utility. Simply knowing that the protein of the present invention is a member of the GPCR family would not provide a utility. The utility of the protein must be known at the time of the present invention.

Applicants argue that in order to demonstrate membership in a class, the law only requires that a class not contain a substantial number of useless members. While this may be true, Applicants have not identified a specific class of compounds to which the present invention belongs. It appears that Applicants are comparing "class" to "the GPCR superfamily." GPCRs are a diverse superfamily of proteins. Opioid receptors, for example, would be expected to have different functions than glutamate receptors, or

thrombin receptors. Therefore, in order for the protein of the invention to have had a specific and substantial or well-established utility, its utility had to have been known at the time of the present invention. Without this knowledge (other than an assumption based on homology), no specific or substantial utility could have been envisioned for this protein. Being a GPCR is not sufficient since numerous proteins are GPCRs. Therefore, this is not a specific utility of the protein of the present invention, nor would simply being a GPCR be a substantial utility in the absence of any other supporting information regarding the biological activity of the protein. Though opioids, glutamate and thrombin receptors are all members of the same superfamily, their divergent properties does not allow one to make specific assumptions about other members of the superfamily. The knowledge, as argued by Applicants, that these proteins transmit signals across plasma membranes is neither specific nor substantial to the protein of the present invention. The Examiner agrees with Applicants that the references cited in the previous Office Action (though not being relied upon or further argued here) at best stand for the proposition that it is difficult to make predictions about function with certainty.

Applicants also argue that Furness Declaration provided support for utility of the present invention. Applicants argue that no biological information is required in using the polynucleotide of the present invention in, for example, toxicology screening, only its identity. While the Examiner does agree that the polynucleotide can physically be used in 2-D gels and Western Blots, the use of this polynucleotide in these assays is, by itself, neither specific nor substantial. It is the information gathered by using hundreds of genes in a toxicology screening assay that provides the artisan with valuable information. This utility of an entire panel of genes for a screening assay does not impart utility for the polynucleotide of the present invention, itself. Furthermore, in the absence of a knowledge of the biological activity of the encoded protein, or in the absence of a knowledge as to what subfamily of receptor this protein belongs, it would not be clear to the artisan how to interpret the toxicology findings. In other words, the artisan would not know if an increase or decrease in gene expression was beneficial or harmful. Therefore, no sound (specific nor substantial) conclusions could be made regarding the toxicity of the drug tested. Furthermore, if a drug had no effect on expression levels of the gene of the present invention, this, again, would provide no valuable information to the artisan as to the specific or substantial role of the gene or encoded protein. Therefore, while a knowledge of biological activity may not be required, what is required is a knowledge of the function of the gene or protein of the invention in order to be able to interpret the findings other than saying, respectfully, that "a drug has an effect on the gene of the present invention, though we do not know what this gene does, other than that is homologous to a known protein." The arguments that a DNA ligase would be presumed to have a ligating function, or that

histones can be used in toxicology testing, are not analogous to the present situation since these examples would assume, or state, that the ligase has been tested for ligase activity and that the histone is, in fact, a histone. The functions of ligases and histones are well-known in the art. No such conclusions were drawn for the protein of the present invention. If the protein of the present invention was shown to have specific thrombin receptor activities, then one may be able to conclude that the receptor is a thrombin receptor.

To summarize, (this argument is also pertinent to Appelants' arguments regarding Coleman '125) all nucleic acids and genes are useful in toxicological testing (this is analogous to 2D-PAGE gels). Therefore, this is a utility which is non-specific and would apply to virtually every member of a general class of materials, such as proteins or DNA. While this may be a well-established use of polynucleotides, it is not a well-established, specific and substantial utility for the polynucleotides of the present invention. Use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array. Applicants' arguments are analogous to saying that a protein with an unknown function which is derived from a rat has utility since rats have utility and this protein is necessary to make a rat. In other words, if the claimed compound is only useful as a larger mixture, then it is the larger mixture that possess the utility. For the reasons stated above in this rejection, the invention is not, at present "practically useful" nor does it confer a "specific benefit" on the public. It is believed that all pertinent arguments have been addressed.

(b) Applicants argue that the rejection of claims 3-7, 9, 10, 12, 13, 57 and 58 under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention, should be withdrawn in view of Applicants' arguments regarding 35 USC 101 above. However, these claims remain rejected for the reasons discussed above.

(c) Regarding the rejection of the claims under 35 USC 112, first paragraph (paragraph (c) above), Applicants argue that claims 4, 5, 10 and 57 do not recite "fragment" or "variant" and should not be included in the rejection. The Examiner agrees. Applicants further argue, however, that a "naturally occurring amino acid sequence" is determined by the process of natural selection and that given SEQ ID NO:1 and 2, the artisan would be able to obtain these natural sequences. Applicants further argue that sequence homology as low as 30% over 150 residues is indicative of protein homology. These arguments have been considered, but are not deemed persuasive. Though, by using PCR and cDNA libraries, the artisan would be able to obtain polynucleotides which hybridize to SEQ ID NO:1 and which encode proteins which have some sequence identity to that of SEQ ID NO:2, the substitution of one amino acid,

or, more likely, the insertion or deletion of 1-5 residues into SEQ ID NO:2, for example, would encompass proteins with functions other than those predicted for SEQ ID NO:2, which itself has no function, as discussed in the above rejection under 35 USC 101. Even, *arguendo*, SEQ ID NO:2 had a known function, this function is not recited in the claims. Therefore, Applicants would not be able to identify a protein other than SEQ ID NO:2 which has a function of SEQ ID NO:2, or which is a naturally occurring variant of SEQ ID NO:2, regardless of its homology. SEQ ID NO:2 is 381 residues. Therefore, there are hundreds of possible combinations of proteins which can have one amino acid substituted, or 1-5 amino acids inserted or deleted. Not only is the breadth of the claims excessive due to this large number of potential variants, but it would not be predictable to the artisan which proteins having these substitutions, insertions or deletions would be naturally occurring variants of SEQ ID NO:2 and which would be similar, but not considered a naturally occurring variant, especially in the absence of the term "variant." In other words, it is not known how these variants are defined.

Applicants have not taught what critical residues make up the functional protein of SEQ ID NO:2, since the function of SEQ ID NO:2 is not known, and, therefore, have not provided and guidance or working examples of naturally occurring variants of SEQ ID NO:2. Applicants further argue that even if these proteins had "absent or altered biological activity" the artisan would know how to use these polynucleotides and that these polynucleotides have a specific, substantial and credible utility. However, the use of polynucleotides which have no utility (as argued above) as probes would not be enabling since Applicants would not know the function of the polynucleotides obtained thru this hybridization.

Regarding 'thrombin-binding fragments" Applicants argue that the specification (pages 23-24) disclose methods of measuring binding to fragments of SEQ ID NO:2 to "any agent which can affect signal transduction." Therefore, Applicants argue that the artisan can make and use the claimed polynucleotides without undue experimentation and that there is no need to identify which residues would need to remain to retain the thrombin-binding characteristics of SEQ ID NO:2. Again, however, Applicants have not provided any guidance or working examples as to which regions of the protein of SEQ ID NO:2 is responsible for its function, especially in light of the fact that the full-length protein has no utility. Given this, the artisan would know which regions of the protein are responsible for a function which has not even been demonstrated for the full-length protein.

Finally, the term "naturally occurring variant" reads on allelic variants of the protein of SEQ ID NO:2. Applicants do not specifically address this issue. However, this issue was discussed on page 7 of the Office Action dated 9/3/02. To reiterate - the Examiner notes, though allelic variants are not specifically defined in the specification, the phrase "naturally occurring TRH," which is defined on page

5 of the specification as "...TRHs produced by human cells that have not been genetically engineered...", reads on allelic variants. The Examiner cannot determine how one would distinguish, merely by examination of the protein, whether a protein were the result of expression of a different allele, or alternatively, were merely one of a number of ultimate species that might be obtained by the expression of SEQ ID NO:1 disclosed in this application. Enablement is not commensurate in scope with claims to proteins potentially encoded for by allelic variants of SEQ ID NO:1, or those of SEQ ID NO:2. Allelic variants often encode proteins with quantitatively or qualitatively altered or absent biological activity. Therefore, the specification does not teach how to use such variants, nor is adequate guidance provided for the skilled artisan to predict, *a priori*, which variants would reasonably be expected to retain biological function.

(d) Regarding the rejection of the claims under 35 USC 112, first paragraph (paragraph (d) above), Applicants argue that there is no statutory requirement that the invention actually be reduced to practice in order for the invention to be patentable and, therefore, they have met the requirement under 35 USC 112, first paragraph, for adequately describing "naturally occurring variants." They further argue that as a result of the degeneracy of the genetic code, a multitude of TRH-encoding nucleotide sequences may be produced and the artisan would recognize whether these are variants of SEQ ID NO:1, or a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:1. Furthermore, Applicants argue that they are in possession of a polynucleotide encoding a protein having one amino acid substitution as well as an insertion or deletion of 1-5 residues.

These arguments have been considered, but are not deemed persuasive. Applicants have not adequately described these variants. There is no definition of what defines a variant of SEQ ID NO:2, especially in light of the fact that the protein of SEQ ID NO:2 lacks utility. The specification provides a written description of SEQ ID NO:2. No other species are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict critical amino acid residues which would structurally characterize the genus of "naturally occurring variants" claimed, because it is unknown and not described what structurally constitutes any different variants; thereby not meeting the written description requirement under 35 USC 112, first paragraph. In addition, the recitation of "naturally occurring variants" reads on allelic variants. Applicants do not specifically address this issue. However, this issue was discussed on pages 9-10 of the Office Action dated 9/3/02. To reiterate - the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1 and 2, the skilled artisan cannot envision the detailed structure of the encompassed

polynucleotides and polypeptides and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polynucleotide or protein itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

The specification discloses only one allele encoding the protein within the scope of the genus: SEQ ID NO:1 for the protein of SEQ ID NO:2. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of the DNA encoding the claimed variants relates to the structure of different alleles. In addition, according to the standard definition, the genus includes members that would be expected to have widely divergent functional properties. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of other unknown alleles having concordant or discordant functions. The common attributes of the genus are not described and the identifying attributes of individual alleles, other than SEQ ID NO:1, or the protein of SEQ ID NO:2, are not described. The nature of alleles is that they are variant structures where the structure of one does not provide guidance to the structure and function of others. According to these facts, one of skill in the art would conclude that the Applicant was not in possession of the claimed genus because a description of only one member of the genus is not representative of the variants of the genus and is insufficient to support the claim.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states

that"An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention." This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Therefore only an isolated DNA molecule comprising a DNA sequence consisting of SEQ ID NO:1 and 2 and equivalent degenerative codon sequences thereof, as well as SEQ ID NO:2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Applicants also argue that the have adequately described "fragments comprising at least 60 contiguous nucleotides of SEQ ID NO:1." However, the claims read that this fragment can be from a naturally occurring variant of the polynucleotide of the present invention. Since the naturally occurring variants lack written description for the reasons provided in this rejection, the claimed fragments of at least 60 contiguous nucleotides also lack written description.

Applicants argue that it would be routine for one of ordinary skill in the art to determine whether any particular fragment of SEQ ID NO:2 has thrombin-binding activity. This argument has been considered, but is not deemed persuasive. First, as discussed in the above rejection under 35 USC 101, Applicants have not demonstrated that this protein is, in fact, a thrombin receptor. Without a showing of utility – that this receptor is, in fact, a thrombin receptor, Applicants are not able to describe which fragments would be required for binding thrombin, nor would the artisan be able to identify thrombin-binding fragments of the protein. The specification does not adequately describe which residues would be required to maintain the thrombin-binding characteristics of the protein. Applicants argue that all that is required is that they show they were in possession of the claimed invention. However, they were not. Applicants were only in possession of one thrombin binding "fragment" – that is SEQ ID NO:2 itself. Again, in other words, the specification provides a written description of SEQ ID NO:2. No other species are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict critical amino acid residues which would structurally characterize the genus of thrombin-binding fragments claimed, because it is unknown and not described what structurally constitutes any different thrombin-binding fragments; thereby not meeting the written description requirement under 35 USC 112, first paragraph. The argument that, in contrast to *Lilly* and *Fiers*, the claims of the present invention define polypeptides in terms of chemical structure, rather than functional characteristics. This is not the case, however, as Applicants are defining thrombin-binding fragments as fragments which have the functional characteristic of binding thrombin.

(e) Claims 4, 5 and 57 remain rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 and 3 of prior U.S. Patent No. 5,686,597. The only difference in the literal claims is the adjective "isolated" vs. "purified." The specification does not define these terms. Both of these claims still evidence the hand of man. Purified is a relative term, and only means 'removed from its natural source', unless otherwise defined in the specification. The New Riverside Dictionary (page 646) defines "isolate" as (1) to set apart from a group or whole. (2) to place in quarantine. (3) to obtain in an uncombined form. (4) to render free of external influence. The Dictionary (page 956) defines "purify" as (1) to rid of impurities. (2) to rid of foreign or unwanted elements. Neither "purified" nor "isolated" specifically mean homogeneous. Therefore, unless otherwise defined, 'isolated' means the same as 'purified', and 'isolated and purified' is merely redundant.

(f) Claims 3, 4, 5, 12, 13 and 57 remain rejected under the obviousness-type double patenting rejection on pages 12-13 of the Office Action dated 9/3/02 as being obvious over claim 1 of patent 5,869,633. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

(g) Claims 3, 4, 5, 12, 13 and 57 remain rejected under the obviousness-type double patenting rejection on pages 13-14 of the Office Action dated 9/3/02 as being obvious over claims 1 and 3 of patent 5,686,597. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

(h) Claim 6 remains rejected under the obviousness-type double patenting rejection on pages 14-15 of the Office Action dated 9/3/02 as being obvious over claim 2 of patent 5,686,597. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

(i) Claims 9 and 10 remain rejected under the obviousness-type double patenting rejection on pages 15-16 of the Office Action dated 9/3/02 as being obvious over claim 6 of patent 5,686,597. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

(j) Claims 6 and 7 remain rejected under the obviousness-type double patenting rejection on page 16 of the Office Action dated 9/3/02 as being obvious over claims 4 and 5 of patent 5,686,597. This rejection will be withdrawn upon filing of a correct Terminal Disclaimer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Robert Landsman

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Conferees

INCYTE GENOMICS, INC.
PATENT DEPARTMENT
3160 Porter Drive
Palo Alto, CA 94304

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600